CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
DICOFOL

Chemical Code # 000346, Tolerance # 0163
SB 950 # 133

July 24, 1986
Revised 3/6/87; 5/12/88; 3/9/90; 10/15/90; 4/6/92; 11/13/92; 5/24/93

I. DATA GAP STATUS

Chronic, rat:	No data gap, possible adverse effect
Chronic, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rodent:	No data gap, possible adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners attached.

In the 1-liners below:
** indicates acceptable study
Bold face indicates a possible adverse effect.
indicates a study/worksheet on file and needs a final review. A preliminary (##) one-liner temporarily entered in the Toxicology Summary and the Data Gap Status (##) may change pending the final review.
File name: T930524
Toxicology summary updated by H. Green and M. Silva, 3/9/90; M. Silva 10/15/90; 3/25/91; Aldous, 4/6/92; Gee, 11/13/92; Kellner, 5/24/93.
Reconciled with library printout of 5/24/93. Summary addresses all reports on file for the above study types. Includes record numbers through 121127 (Document No. 163-121), plus some record

numbers of the 900000+ series.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

NOTE: The most recent studies were performed using a new, more refined technical material with reduced levels of DDT and certain DDT analogs.

COMBINED RAT

****083, 087 074659, 091360**, "Dicofol (Kelthane® Technical Miticide): 24-Month Dietary Chronic/Oncogenic Study in Rats", (Quinn, D.L. and Hazelton, G.A., Rohm and Haas Co., Toxicology Department, PA., report # 86R-190, 3/29/89). Dicofol (Kelthane® Technical Miticide; 93.3% pure; lot # RS-4503; brown solid) was fed in the diet for 24 months at mean analytical concentrations of 0, 4.52, 45.32, and 238.70 ppm to 100 CRL:CD® BR rats/sex/group. Interim sacrifices (10/sex/group) were performed at 3, 12, and 18 months. Possible **adverse effects** indicated. Chronic Toxicity NOEL = 4.52 ppm (0.22 mg/kg/day in males and 0.27 mg/kg/day in females). Hepatocellular necrosis, vacuolation, hyperplasia, and hypertrophy were observed in both sexes at $\geq$ 45.32 ppm (visible from 3 months). Diffuse vacuolation of adrenal cortical cells was observed in 238.70 ppm females at 3 and 12 months; in 45.32 ppm and 238.70 ppm females at 18 months; and in 238.70 ppm males and females at 24 months. No oncogenicity was observed. Previously reviewed as unacceptable (H. Green & M. Silva, 2/28/90). Upgraded to ACCEPTABLE upon submission of information showing that histopathology was performed on all terminal sacrifice animals in the high dose and control groups**.** (M. Silva, 10/3/90).

063 060292 "Kelthane: Three-Month Dietary Toxicity Study in Rats," (Rohm & Haas Company, 2/21/86). Kelthane technical (Lot No. MLO-0953, TD No., 84-393) was administered in diet to 10 Crl-CD (SD) BR rats/sex/group at 0, 1, 10, 100, 500 and 1500 ppm for 13 weeks. **Possible adverse effect.** NOEL = 1 ppm (at 10 ppm and above, increased incidence and severity of hypertrophy of thyroid follicular epithelial cells; at 100 ppm and above - hepatocellular hypertrophy, increased MFO and liver weight; at 500 ppm and above - hepatocellular necrosis, diffuse enlargement and vacuolation of the cortical cells in the adrenals, decreased serum corticosterone levels, at 1500 ppm - enlarged and darkened livers and small spleens; increased intensity of multifocal-myocarditis, ventricular dilatation and myocardial fibrosis). The study is a supplementary to the lifetime rat study 074659. M. Silva, 5/5/88.

064 060295 "Dicofol (Kelthane Technical Miticide): 24 Month Dietary Chronic/Oncogenic Study in Rats - Status Report," Rohm & Haas Company, Springhouse, PA, 12/4/86; Dicofol (93.3%, lot# RS-4503, <0.1% DDTr) at 0, 5, 50 or 250 ppm was fed to 60 rats (strain not specified)/sex/group. Additional animals (10/sex/group) were fed treated diet for interim necropsies at 3, 6, 12 & 18 months. (Nominal dose) NOEL = 5 ppm (Increased relative liver weights at 50 & 250 ppm and kidney weights at 250 ppm). **Possible adverse effect** (liver cell hypertrophy with necrosis of single or small groups (multifocal) of hypertrophied hepatocytes at 50 & 250 ppm; liver and adrenal cell vacuolation in both sexes). This report is a summary of a 3-month analysis update. M. Silva, 5/11/88.

002 043629 "Toxicologic Studies on 1,1-bis-(chlorophenyl)- 2,2,2-trichloroethanol (Kelthane)."

(Publication in: Toxicology and applied Pharmacology 1 : 119 - 134 (1959)). Two-year dietary administration to rats at 0, 20, 100, 250, 500 or 1000 ppm; 10/sex/group; decreased weight gain in females at 250 ppm and higher, in males at 500 and 1000 ppm; increased liver:body ratio in females at 250 and higher and 500 ppm and higher in males; NOEL = 100 ppm. UNACCEPTABLE (inadequate number of animals, incomplete.) J. Gee, 2/26/87.

002 043630 "Toxicologic Studies on 1,1-bis-(chlorophenyl)-2,2,2-trichloroethanol (Kelthane)." (Publication in: Toxicology and Applied Pharmacology 1: 119 - 134 (1959)). Fifty-five week oral feeding study in rats; 15/sex/test group and 25/sex for controls; fed 0, 2, 5, 10, 15 or 20 ppm Kelthane; liver:body weight the only parameter presented; no dose-related findings reported. UNACCEPTABLE (number of animals, incomplete). J. Gee, 2/25/87.

CHRONIC, DOG

**081 072889, "Dicofol (Kelthane® Technical Miticide): One-Year Dietary Toxicity Study in Beagle Dogs", (Tegeris Laboratories, Inc., report # 86014, 12/14/88). Dicofol (Kelthane® Technical Miticide; 93.3% pure; Lot # RS-4503, TD # 85-211) was fed to Beagle dogs (6/sex/group) in the diet for one-year at mean analytical concentrations of 0 (vehicle = acetone), 4.76, 29.54, 177.03, and 183.27 ppm. A recovery group was fed diet containing 183.27 ppm during weeks 1 through 14, then 0 ppm thereafter. Increased SAP values in 177.03 ppm males at weeks 13, 26, and 39. No adverse effects. NOEL = 29.54 ppm (Increased male liver weights were observed at 177.03 ppm. Histopathology of 177.03 ppm animals revealed 5 of 6/sex/group with minimal to mild hypertrophy of hepatocytes). NOAEL > 183.27 ppm (no adverse effects were observed at any dose). ACCEPTABLE. (H. Green & M. Silva, 3/2/90).

062, 060291 "Three Month Dietary Toxicity Study in Dogs with Dicofol (Kelthane Miticide)," Tegeris Laboratories, Laurel, Maryland, 11/26/86. Dicofol (93.3%) was administered in diet to 6 dogs/sex/group at 0, 10, 100, 300 or 1000 ppm for 90 days. (Nominal dose) NOEL = 10 ppm (Clinical chemistry and blood parameters were altered significantly and ECG tracings showed prolongation of QT and PR intervals at and above 300 ppm; mean plasma cortisol was significantly decreased at and above 100 ppm; at 1000 ppm gross lesions, hemorrhage, lumenal blood in GI tract as well as 5 deaths/sex were observed.) **Possible adverse effect**. Hepatic necrosis and hydropic degeneration as well as myocardial necrosis occurred at 1000 ppm. Males experienced oligospermatogenesis at 300 and 1000 ppm. This is supplementary to the chronic dog study [081 072889, above]. M. Silva, 5/11/88.

002 043627 "Toxicologic Studies on 1,1-bis-(chlorophenyl)-2,2,2-trichloroethanol (Kelthane)." (Publication in: Toxicology and Applied Pharmacology 1: 119-134 (1959)). One-Year dietary administration to dogs, 3 per diet level, at 0, 100, 300 or 900 ppm; no effects reported. UNACCEPTABLE (number of animals, incomplete). J. Gee, 2/26/87.

ONCOGENICITY, RAT (See also combined rat, above)

012 921740 "Bioassay of Dicofol for Possible Carcinogenicity." (1978, National Cancer Institute, No. 90, publ. No. (NIH) 78-1340). Technical dicofol (40-60%) in the diet at 471 or 942 ppm to groups of 50 males or at 380 or 760 ppm to group 50 females (time weighted averages); vehicle control (20/sex) for 78 weeks followed by 34 weeks of observation; Small increase in the numbers of liver tumors (malignant) and thyroid carcinomas but not statistically significant by Fisher's exact test; UNACCEPTABLE study due to major variances (only 2 dose levels, variable dose levels, too few control animals) but useful information. Not upgradeable. Initial review by J. Wong indicated a possible oncogenic effect (see above) but review by J. Gee, 7/31/86, notes that neither tumor type is increased with statistical significance in the rat. J. Wong, 5/1/85.

037 036108 Duplicate of 921740.

ONCOGENICITY, MOUSE

**** 012, 064 921740, 022845, 038515, 060296, 058209** "Bioassay of Dicofol for Possible Carcinogenicity," (1978, conducted at Hazleton Laboratories for the National Cancer Institute, No. 90, publ. no. (NIH) 78-1304). Technical dicofol (report states 40-60% purity but analytical data in volume/record#: 064 060296 showed purity of technical to be 96.09 to 97.86%) was administered in the diet at 471 or 942 ppm to B6C3F1 male mice (50/group) or to females at 122 or 243 ppm (50/group: time weighted averages) and vehicle control (20/sex) for 78 weeks followed by 15 weeks of observation. **Possible adverse effect.** Dose related increases in lung and liver tumors were observed. Incidence of liver tumors in males: control, 3/18; low dose, 22/48; high dose, 35/47. See comments below. Original review (J. Wong, 5/1/85) classified study as unacceptable and not upgradeable (only 2 dose levels, variable dose levels, too few control animals, no individual data). After an additional review of individual data on male livers (volume/record#: 044 50748) there was no change in adverse effect status on liver but the lesions were defined as adenomas rather than carcinomas. J. Gee, 3/5/87. Subsequently, additional clinical records (volume/record#: 064 058209) and a pathology summary table requested by CDFA were received and reviewed. It is now considered that the major deficiencies in this study have been addressed and therefore the study is ACCEPTABLE. M. Silva, 5/5/88.

030 026967, 026968. Supplement to 921740, 022845, 038515, 060296, 058209.

037 036107 Duplicate of 921740

044 050748 Supplement to 921740 with additional review of male mouse liver data.

030 026973, -70, -69, -71, and -72 "Panel Review of the Carcinogenicity of Dicofol and Related Compounds." (1978) Supplementary comments on 921740, 832 oncogenicity study in mice. Review of the liver slides for pathological findings. The initial report contains data indicating hepatocellular carcinoma in males due to dicofol. Interpretation by three pathologists concludes the liver changes are either adenomas or hyperplastic nodules -- not metastatic carcinomas -- based on the lack of metastases and no abnormal trabecular pattern associated with potential for metastasis. The studies, however, confirm chronic liver toxicity of the chlorinated hydrocarbon which needs evaluation. J. Gee, 7/28/86.

064 060294 "Liver MFO Assays for Kelthane Technical, its Active Ingredients, and Principal Technical Impurities in Male B6C3F1 Mice After Two Week Dietary Exposure," (Rohm & Haas, Spring House, PA, 5/1/84). Kelthane technical, the two active ingredients in Kelthane (p,p'-dicofol and o,p'-dicofol) and six contaminating analogs found as impurities in Kelthane were fed in diet to male B6C3F1 mice (4/group) for two weeks. Dose levels were: Kelthane 0, 8, 25, 80, 250 and 800 ppm; p,p'-dicofol 0, 6, 20, 63, 195 and 625 ppm; o,p'-dicofol, p,p'-DDE 37.5 ppm; p,p'-DCBP 20, 63 and 195 ppm and o,p'-DCBP 195 ppm. No adverse effect**.** NOEL Kelthane = 25 ppm (increased MFO activity, liver weight, liver to body weight ratio above 80 ppm; decreased body weight above 25 ppm.) NOEL p,p'-dicofol = 20 ppm (increased MFO activity above 20 ppm, increased liver weight and liver to body weight ratio as well as decreased body weight above 195 ppm.) NOEL for all other compounds was greater than the highest levels tested. Technical Kelthane activity is apparently due principally to the major active ingredient p,p'-dicofol. Supplementary to 030 0296969-73. M. Silva, 5/11/88.

061 060290 "Dicofol (Kelthane Technical Miticide): Three Month Dietary Toxicity Study in Mice," (Report No. 85R-104) Rohm & Haas Company, Toxicology Department, 11/86). Kelthane Technical was administered in diet for three months to CD-1 mice (20/sex/group) at 0, 10, 125, 250, 500 and 1000 ppm. NOEL = 10 ppm (increased liver weight and MFO activity, decreased body weight at 125 ppm and above; decreased kidney weight). **Adverse effect indicated** (centrilobular hepatocellular hypertrophy at 250 ppm and above; dilated and/or pale kidneys with gross dilatation and degeneration of cortical tubules and other renal lesions; diffuse hypertrophy of cells of adrenal cortex, enlarged livers with prominent architecture, pale and granular, necrosis and vacuolation of hypertrophied hepatocytes at 500 ppm and above). Supplementary to lifetime mouse study (012 921740). M. Silva, 5/11/88.

064 060297 "Mouse Liver Mixed Function Oxidase Assay for Kelthane Technical: Three Day po Induction Study," (Rohm & Haas Company, 4/2/84). Kelthane technical (TD, lot no. 1906, 87.6% a.i.) was administered by gavage for three days in doses of 0 (vehicle = corn oil), 1.4, 4.4, 14.9, 42.8 or 151 mg/kg to 4 CD-1 mice/sex/group. No adverse effect**.** NOEL = 4.4 mg/kg (Liver weight increased significantly in both sexes at 14.9 mg/kg; liver to body weight ratio increased in males at 42.8 and 151 mg/kg and in females at 151 mg/kg; MFO activity increased in females at 14.9 mg/kg and above.) Supplementary to lifetime mouse study (012 921740). M. Silva, 5/11/88.

037 036110 Copy of Federal Register Vol. 50, No. 158, August 15, 1985, with EPA's comments on Dicofol.

037 036109 Supplemental oncogenicity information.

REPRODUCTION, RODENT

****163-092 089213** Solomon, H.M. and Kulwich, B.A., "Dicofol: Two-Generation Reproduction Study in Rats", Rohm & Haas Company, Toxicology Department, Report No. 89R-028, 2/18/91. Kelthane Technical, purity 93.3%, was administered in the feed at concentrations of 0, 5, 25, 125, or 250 ppm/day to two generations (1 and 2 litters for the first and second generations, respectively) of 25 Crl:CD*BR rats/sex/group. Parental NOEL = 5 ppm (increase in incidence and degree of centrilobular hepatocytic hypertrophy, dose-related in both sexes and in both

generations). Other important parental effects were hepatocyte vacuolation at 25 to 250 ppm in males, hypertrophy of the inner cortex of the adrenals (125 and 250 ppm females), and increased vacuolation of ovarian stromal cells (marked in 250 ppm females, lesser increases at 25 and 125 ppm). P1 adult body weights were reduced by about 10% in both sexes at 250 ppm and in females at 125 ppm, but there were no body weight effects in the F1 generation parents. Reproductive NOEL = 25 ppm (decreased pup survival during days 0-4). Increased stillbirths and decreased pup weights during lactation were noted at 250 ppm in both generations. ACCEPTABLE**, with possible adverse effect (based primarily on reduced pup survival during early lactation).** (Kishiyama and Aldous, 4/6/92)

163-088 091538 Data accompanying an "adverse effects disclosure" letter for the reproduction study, which was subsequently completed as 163-092 089213, above. Preliminary results were summarized as the following effects: increased stillbirths at 250 ppm, offspring mortality at 125 and 250 ppm, and histopathologic changes in ovaries at 250 ppm. See review of final report for details of study. Aldous, 4/6/92.

037 036113, 036111, 036112 "Toxicologic Studies on the Effects of Kelthane in the Diet of Albino Rats on Reproduction" (Univ. of Toronto, 1965). Dicofol technical, 84.7%; 27/sex/group were fed 0, 100, 500 or 1000 ppm in the first study and 0, 25, 75 or 225 (1 generation) in second study; **adverse reproduction effect** at 500 & 1000 ppm in first part, at 225 in second: reduced litter number produced, reduced pup survival; estimated NOEL: 75 ppm; incomplete (no analysis of diet, no justification of dose selection, inadequate individual data - body weights, food consumption, not all required tissues/organs for histopathology, low survival in control pups as well as in treated groups). Part 2 of interim Report, Record # 036112, contains a notation that fecundity problem was likely due to "deficient" diet. This seriously compromises the study. Part II, Record # 036112, contains a summary statement that "original" rats were sacrificed after 9 months on 100, 500 or 1000 ppm diets and 61 animals in total were examined from all groups with no morphological changes noted. The number per dose group, however, is not given for comparison. While ovaries and testes appeared normal, 1000 ppm-group rats did not produce litters. UNACCEPTABLE. Not upgradeable. J. Gee, 7/14/86.

037 036119, 036115 "Three Generation Reproduction Study on Rats Receiving Technical Kelthane in their Diet." (Univ. of Toronto, 1967) Dicofol (84.8%, technical lot 2588); 14-24 male/females per group fed 0, 25 or 75 ppm in the diet; 3 generations with 2 litters each plus a repeat FO to F1A, F1B at 0 & 25 ppm due to low viability index in all groups; No maternal/paternal effects reported: NOEL > 75 ppm; reduced pup weaning weight at 75 ppm (-9%): reproductive NOEL = 25 ppm. **Possible adverse effect.** UNACCEPTABLE, not upgradeable (no individual data, no analysis of diet, inadequate histopathology with 15/sex of F3b offspring only, no pup weights at days 0, 4, 7 or 14 for evaluation, mixed matings of females with males being rotated "at frequent intervals." J. Gee, 7/14/86.

037 036114, 036120 "Toxicologic Studies on 2,2-bis-(chlorophenyl)-2,2,2,2-trichloroethanol (Kelthane): The Effect of Dietary Kelthane on Mouse Reproduction." (Brown Biol. Lab., 1967) Dicofol lot 2588, 84.8%; 41-47 pairs/mating; 5 generations with 2 litters each; fed at 0, 7, 25, 100, 225 or 500 ppm. Diets prepared weekly and the remainder discarded; NOEL = 225 ppm (decreased litter size at birth and 21 days, decreased pup weight at 21 days), no parental effects; incomplete (missing info.). **Possible adverse effect.** UNACCEPTABLE (no analysis of diet presented, inadequate pathology presentation with half-page summary for all siblings, all

generations, no individual data, no pup weights on days 0, 4, 7 or 14, males and females housed together from mating through weaning of pups.) J. Gee, 7/14/86.

TERATOGENICITY, RAT

**043 050747 "Kelthane Technical B: A Developmental Toxicity Study of Dicofol (Kelthane [Technical] Miticide) Administered Via Gavage to Crl:COBS CD(SD) BR Presumed Pregnant Rats." (7/3/86, Argus 86RC0069) Kelthane technical, Lot ML0-0953, 95.6% purity, tested at 0, 0.25, 2.50 and 25.0 mg/kg/day by oral gavage, days 6-15 gestation to 25/group Crl:COBS CD(SD) BR rats; maternal NOEL (increased salivation, decreased b. w. and feed consumption/efficiency and liver effects) = 0.25 mg/kg/day and developmental NOEL > 25 mg/kg/day; ACCEPTABLE J. Parker 2/24/87.

TERATOGENICITY, RABBIT

**042 050746 "Kelthane Technical B: A Developmental Toxicity Study on Dicofol Administered Via Stomach Tube to New Zealand White Rabbits." (5/28/86, Argus 86RC0015). Kelthane technical, Lot MLO-0953, 95.6% purity; tested at 0, 0.4, 4.0 and 40.0 mg/kg/day by oral gavage day 7 through 19 to 20/group NZW rabbits; maternal NOEL (reduced body weight and increased liver histopathology) = 0.4 mg/kg/day and developmental NOEL > 40 mg/kg/day; ACCEPTABLE. J. Parker 2/24/87.

MUTAGENICITY, GENE MUTATION

044 050749 "Kelthane Technical: Microbial Mutagenicity Assay." (Rohm & Haas, Spring House, PA, 7/26/85 Salmonella (TA 1535, TA 1537, TA 98 & TA 100); dicofol (95.6%); 0, 20, 50, 200, 500, 2000 or 5000 ug/plate with & without activation; toxicity at higher concentrations in some strains; UNACCEPTABLE (no positive controls without activation.) No evidence for increase in reversion rate. J. Gee, 7/14/86.

037 036116 Incomplete version of 050749.

**039 043794 "Kelthane Technical CHO/HGPRT Gene Mutation Assay." (Rohm & Haas Co., Toxicology Dept., Spring House, PA, 3/27/86). Chinese Hamster Ovary Cells; plus and minus rat liver activation; Kelthane technical (95.6%) at 0, 3, 4, 4.5, 5 or 6 ug/ml (minus S9) or 0, 4.5, 10, 12, 15, 17 or 20 ug/ml (plus S9); high concentration determined by cytotoxicity; minimum of 2 trials; no consistent increase in mutation frequency; Complete and ACCEPTABLE. J. Gee 7/28/86.

018 039644, 039645, 039646 References to various studies. No data.

MUTAGENICITY, CHROMOSOME

**064 060293 "Clastogenic Evaluation of Kelthane Technical (TD 84-393 Lot #MLO 0953 Rohm

& Haas Protocol No. TD85-346) in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells," Litton Bionetics, Kensington, MD, 7/86. Dicofol (95.6%) at 7.5, 10.0, 15.0 or 20.0 ug/ml was added to CHO cells with or without rat liver S-9. A statistically significant increase in percent of cells with aberrations was observed at 20 ug/ml with activation, but was not confirmed in a repeat assay, where activation and dose levels of 17.5, 20.0, 22.5 & 25.0 ug/ml gave no increase in numbers of cells with aberrations. No adverse effect. ACCEPTABLE. M. Silva, 5/11/88.

163-091 096355 Duplicate of 060293.

**039 043795 "Kelthane In vivo Cytogenetic Study in Rats." (Rohm & Haas, Spring House, PA, 3/26/86). In Vivo Cytogenetic Study in Rats; Kelthane technical (95.6%) at 50, 200 or 500 mg/kg by oral gavage to 10 males per group with sacrifice at 6, 24 or 48 hours; TEM for positive control; no evidence of chromosomal aberrations related to treatment. Analysis of the solution indicated actual content was 44,600 ppm so high dose was actually 446 mg/kg body weight. The LD50 is stated as 595 mg/kg. High dose caused clinical signs. Initial review found the study unacceptable but upgradeable with the justification for using males only. In the rebuttal contained in Document 163-044, dated 11/24/86, the use of only males is justified based on comparable LD50's for both sexes and comparable half-lives for elimination. This information provides assurance that there is not likely to be a qualitative difference between the sexes. ACCEPTABLE. J. Gee, 7/28/86.

018 039647, 039648 Summary information.

MUTAGENICITY, DNA/OTHER

**039 043796 "Kelthane Technical In vitro Unscheduled DNA Synthesis Assay." (Rohm & Haas, Spring House, PA, 1/31/86) Unscheduled DNA Synthesis: Rat Hepatocytes; Exposed 18.5-19.5 hours to 0, 0.025, 0.05, 0.10, 0.25 or 0.5 ug/ml (level of cytotoxicity: 0.25 ug/ml); no evidence of UDS response. Complete & ACCEPTABLE. J. Gee, 7/28/86.

MUTAGENICITY, SUPPLEMENTAL

037 047073 Literature/study review of dicofol mutagenicity.

NEUROTOXICITY

**163-121 121127 "Acute Neurotoxicity Study of Dicofol (Kelthane® Technical B Miticide) Administered Orally Via Gavage to Crl:CD®BR VAF/Plus® Rats", (J.A. Foss, Argus Research Laboratories, Laboratory Project ID ARL, Protocol 018-017, 10/2/92). Dicofol, 95.5% A.I. was administered (oral-gavage, single dose) at 0 (control), 15, 75 or 350 mg/kg to 10 Sprague-Dawley rats/sex/group. Treatment related effects beginning 1 day after dosage included effects on motor activity (decreases in the number and time of movements in the high-dose group). In the functional observational battery (FOB) tests, increased incidence of ataxia and decreased rearing and air righting performance for high-dosed males and increased ataxia, tip-toe walking,

soft/liquid feces and sleeping appearance for high-dose females were noted; urine/fecal stains on the fur increased (both sexes) in the high-dose group. Other effects included reduced food consumption, body weight and body weight gains for mid- and high-dose groups. Rats were apparently normal after two weeks. NOEL (systemic toxicity) = 15 mg/kg. **No adverse neurotoxic effects.** ACCEPTABLE. Kishiyama, Kellner and Gee, 4/21/93.

163-116 116942 "HEAR Report of Treatment-Related Effects Observed in an Acute Neurotoxicity Evaluation of Dicofol (Kelthane Technical B Miticide)." (Argus Research Laboratories, PA, 6/29/1992) Dicofol (Kelthane), purity not stated, was given as a single oral dose to rats, 10/sex/dose, at 0 (corn oil), 15, 75 and 375 mg/kg. Motor activity was measured by a "computerized device" at 8 and 24 hours, 7 and 14 days. Motor activity (total number of movements over 90 minutes) was decreased at the high dose of 375 mg/kg at 24 hours. There was an apparent recovery at 7 and 14 days. Clinical observations at 375 mg/kg included tip-toe walk, feces-stained fur, ataxia, soft or liquid feces, impaired righting reflex and decreased motor activity. All were normal by day 14. Two pages of unaudited tables were submitted as an adverse effects disclosure. Histopathology is in progress. Full report due in 1992. (Gee, 11/13/92)

STUDY SCHEDULE FOR KELTHANE MITICIDE (DICOFOL): SEE VOLUME 163-037.